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(72) Inventors:
• Pellico, Michael A.
Santa Monica, CA 90402 (US)
• Kang, Harjinder
Rancho Dominguez CA 90220 (US)

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(74) Representative: Matthews, Howard Nicholas et al
Prentice & Matthews,
Calvert's Buildings,
52 B Borough High Street
London SE1 1XN (GB)

(71) Applicant: Laclede, Inc.
Rancho Dominguez, California 90220 (US)

(54) Aqueous enzymatic denture adhesives

(57) Hydro-activated and/or oxygen activated aqueous, enzymatic, antimicrobial denture adhesive compositions are stabilized against enzymatic action prior to oral application of the adhesive by incorporating a thickener into the adhesive formulation so as to provide the formulation with an enzyme immobilizing viscosity which inhibits enzymatic action during processing and in the adhesive package. An illustrative, thickened, en-

zymatic adhesive with this enhancement contains glucose oxidase, glucose, lactoperoxidase and potassium thiocyanate together with a mixture of polyacrylic acid and polyvinylpyrrolidone in an amount to provide the adhesive with a viscosity of at least about 300,000 centipoises.

EP 1 334 710 A1

Description

1. FIELD OF THE INVENTION

[0001] This invention relates to enzymatic denture adhesive compositions and, more particularly, to stabilized, aqueous, enzymatic denture adhesives, which, upon oral application, produce an anti-bacterial and bacteriostatic effect in the oral cavity by activation of the enzyme system within the adhesive.

[0002] Denture adhesives are used by denture wearers to secure loose fitting dentures. When a denture is first made, it fits tightly in the mouth. However, with the passage of time, the mouth changes and the denture often becomes less secure, with loss of the initial tight fit.

[0003] When this occurs, the patient has three choices: (a) obtain a new denture, (b) reline the old denture, or (c) use a denture adhesive. For those who choose denture adhesives, there are diverse products from which a selection can be made. These include powders, gels, pastes, and sheets. The adhesives are based on water soluble gums and polymers such as carboxymethyl cellulose, gum aracia, gum tragacanth, poly(ethylene oxide), polyvinylpyrrolidone, vinyl methyl ether maleic anhydride, polyacrylamides, acetic polyvinyl compounds, polyacrylic acid derivatives and the like.

[0004] The most common denture adhesives are those sold as pastes. The pastes are usually a combination of gums and powders combined with oil and/or other vehicle. The denture wearer squeezes the paste from a dispensing tube onto the denture which is then fitted into the mouth. Denture powders based on gums and/or polymers are also widely used by sprinkling the powder onto the denture which is then positioned in the mouth. Denture adhesives are also sold as sheets or films prepared from gums or polymers.

[0005] Regardless of the physical form of these adhesives, they all require contact with water to become effective. It is only when the gums and polymers become wet that they develop their adhesive properties. Normally, these adhesives work very well in the mouth. However, for denture wearers who suffer from dry mouth (xerostomia), dentures adhesives work poorly or not at all because there is insufficient saliva to activate these adhesives. Also, because saliva is naturally antibacterial, people who suffer from dry mouth have an increased risk of periodontal disease, cavities and mouth odors.

[0006] The invention herein is directed to water-based denture adhesive compositions which incorporate (a) a hydro-activated anti-bacterial enzyme system and (b) a thickener so as to provide the composition with an enzyme immobilizing viscosuity to inhibit enzymatic action during processing and in the denture adhesive package prior to oral application. The aqueous denture adhesive, with its anti-bacterial system, is particularly well suited for denture wearers who suffer from impaired saliva flow and provides those denture users with oral protection that would otherwise be present with normal saliva flow.

2. RELATED ART

2A. ENZYME SYSTEMS

[0007] It is disclosed in the prior art that enzymatic anti-bacterial systems, predicated on oxidoreductase enzymes such as glucose oxidase, can be incorporated into oral care products and other products such as powder milk (U.S. Patent No. 4,617,190) and bandages (U.S. Patent No. 4,576,817) for producing an anti-bacterial effect in a defined environment.

[0008] U.S. Pat. No. 4,150,113 (Hoogendoorn et al., 1979) and U.S. Pat. No. 4,178,362 (Hoogendoorn et al., 1979) disclose, respectively, an enzymatic toothpaste and an enzymatic chewable dentifrice containing glucose oxidase which acts on glucose present in saliva and tooth plaque to produce hydrogen peroxide. The patentees note that oral bacteria, through enzyme systems having SH-Groups, effect glycolysis of food products containing sugars and point out that lactoperoxidase, which is present in saliva, provides the means for transferring oxygen from hydrogen peroxide to oral bacteria resulting in the oxidation of the SH-containing enzymes into inactive disulfide enzymes. It is further disclosed that the dentifrice may be formulated with potassium thiocyanate.

[0009] U.S. Pat. No. 4,269, 822 (Pellico et al., 1981) discloses an antiseptic dentifrice containing an oxidizable amino acid substrate and an oxidoreductase enzyme specific to such substrate for producing hydrogen peroxide and ammonia upon oral application of the dentifrice, with pre-application stability being maintained by limiting the quantity of any water present in the dentifrice.

[0010] U.S. Pat. No. 4, 537, 764 (Pellico et al., 1985) discloses an enzymatic dentifrice containing Beta-D-glucose and glucose oxidase for producing hydrogen peroxide upon oral application of the dentifrice, with pre-application stability being maintained by limiting any water in the dentifrice to not more than about 10 wt.% based on the weight of the dentifrice.

[0011] U.S. Pat. No. 4,564,519 (Pellico et al., 1986) discloses a di-enzymatic chewable dentifrice which contains,

for example, glucose and glucose oxidase for producing hydrogen peroxide upon chewing the dentifrice and further contains a thiocyanate salt and lactoperoxidase for interacting with hydrogen peroxide to produce a hypothiocyanate (sic) bacterial inhibitor, with pre-application stability being maintained by limiting any unbound water in the chewable dentifrice to an amount not more than about 1.0 wt.% and limiting the total water, bound and unbound, to not more than about 10 wt.%.

[0012] U.S. Pat. No. 4,578,365 (Pellico et al., 1986) discloses a di-enzymatic dentifrice which contains, for example, glucose and glucose oxidase for producing hydrogen peroxide upon oral application of the dentifrice and further contains a thiocyanate salt and lactoperoxidase for interacting with hydrogen peroxide to produce a hypothiocyanate (sic) with pre-application stability being maintained by limiting any water in the dentifrice to not more than about 10 wt.% based on the weight of the dentifrice.

[0013] U.S. Patent No. 5,176,899 (Montgomery, 1993) discloses an aqueous enzymatic dentifrice which contains, for example, Beta-D-Glucose and glucose oxidase for producing hydrogen peroxide upon oral application of the dentifrice and, optionally, contains a thiocyanate salt and lactoperoxidase for interacting with hydrogen peroxide to produce a hypothiocyanate (OSCN-) bacteriostatic agent, with pre-application stability being maintained by processing and packaging the dentifrice under vacuum conditions so as to limit the level of dissolved oxygen in the dentifrice.

[0014] U.S. Pat. No. 5,336,494 (Pellico, 1994) discloses an orally chewable, enzymatically coated pet product which contains, for example, Beta-D-glucose and glucose oxidase for producing hydrogen peroxide upon oral chewing of the product and may further contain a peroxidase and an alkali metal salt of an oxygen accepting anion such as potassium iodide for interacting with hydrogen peroxide to produce hypodilite, an anionic bacterial inhibitor.

[0015] U.S. Pat. No. 5,453,284 (Pellico, 1995) discloses an aqueous enzymatic dentifrice having a water content in excess of 10 wt. % and which contains, for example, Beta-D-glucose and glucose oxidase for producing hydrogen peroxide upon oral application of the dentifrice and may further contain a peroxidase and an oxidizable alkali metal salt such as the thiocyanate, chloride or iodide salt of sodium or potassium for interacting with hydrogen peroxide to produce an anionic bacterial inhibitor, with pre-application stability being maintained by the addition of a water soluble thickener in an amount to provide the dentifrice with a viscosity from about 800 to about 75,000 centipoises.

2B. DENTURE ADHESIVES

[0016] U.S. Patent No. 4,518,721 (Dhabhar et al., 1985) discloses a hydrophillic denture adhesive containing sodium carboxymethylcellulose, poly(ethylene oxide), polyethylene glycol and glycerin.

[0017] U.S. Patent No. 4,804,412 (Komiya, 1989) discloses a denture adhesive containing polyvinyl acetate and polypropylene oxide and which may further include other ingredients such as enzymes, as for example, dextranase, mutanase, levanase and in(s)ulinase.

[0018] U.S. Patent No. 5,760,102 (Hall et al., 1998) discloses an aqueous denture adhesive containing also extract, polyvinylpyrrolidone, hydroxyethylcellulose, hydrogen peroxide and water.

[0019] U.S. Patent No. 6,294,594 (Borja, 2001) discloses a denture cream formulation containing polyvinylpyrrolidone, poly(ethylene oxide), carboxymethylcellulose, mineral oil, petrolatum, polyacrylic acid derivative, silicon dioxide, flavor and dye.

[0020] Each of the foregoing patent references is incorporated herein by reference thereto.

SUMMARY OF THE INVENTION

[0021] In accordance with this invention, there is provided an aqueous enzymatic denture adhesive having a water content of at least about 10 wt. % and containing, per gram of adhesive, from about 0.015 to about 0.6 millimole of oxidizable substrate and from about 0.5 to about 5,000 International Units of oxidoreductase enzyme specific to such substrate for producing hydrogen peroxide upon oral application of the adhesive, and further containing non-toxic, ambient, water soluble thickener in an amount to provide the adhesive with a viscosity from about 300,000 to about 1,900,000 to thereby stabilize the adhesive against the production of hydrogen peroxide prior to oral application of the adhesive.

DETAILED DESCRIPTION

[0022] The invention described herein is directed to the use of thickener in aqueous denture adhesive compositions containing hydro-activated and/or oxygen activated anti-bacterial enzyme system to thereby provide a viscosity which inhibits the enzymatic reaction prior to oral application of the adhesive.

[0023] The thickeners which can be used in the practice of this invention comprise non-toxic, water soluble hydrocolloids and synthetic polymers as, for example, (a) water soluble gums such as gum arabic, gum tragacanth, gum karaya or gum guar; (b) microbial fermentation hydrocolloids such as xanthan gum; (c) starch derivatives such as high

viscosity starch or hydrogenated starch; (d) cellulose derivatives such as sodium carboxymethylcellulose or hydroxymethylcellulose; and (e) synthetic polymers/gums including (i) vinyl polymers such as polyvinylpyrrolidone, polyvinyl alcohol and carboxyvinyl polymer, (ii) acrylic polymers such as polyacrylic acid and polyacrylamide, and (iii) ethylene oxide polymers. A particular effective thickener is a combination of polyacrylic acid and polyvinylpyrrolidone which may be further enhanced by the presence of hydrogenated starch.

[0024] The thickener is generally present in an amount to provide the enzymatic denture adhesive with a viscosity from about 300,000 to about 1,900,000 centipoises, with an intermediate amount being so selected as to provide the adhesive with a viscosity from about 400,000 to about 1,750,000 centipoises, and a preferred amount being so selected as to provide the adhesive with a viscosity from about 600,000 to about 1,600,000 centipoises. Viscosity determinations may be made by utilizing a suitable viscometer in accordance with applicable procedures well known in the art.

[0025] The enzymatic component of the therapeutic composition comprises a first enzyme system containing an oxidizable substrate and an oxidoreductase enzyme specific to such substrate for producing hydrogen peroxide upon oral application of the adhesive, with the chemical environment of the oral cavity providing the source of additional reactant (oxygen) or reactants (oxygen, water) to effect the enzymatic reaction. Illustrative examples of oxidoreductase enzymes and their corresponding oxidizable substrates are set forth in the following table:

TABLE A

OXIDOREDUCTASE ENZYME	OXIDIZABLE SUBSTRATE
Glucose oxidase	B-D-glucose
Hexose Oxidase	Hexose
Galactose Oxidase	D-galactose
Pyranose Oxidase	Pyranose
Pyruvate Oxidase	Pyruvate
Oxalate Oxidase	Oxalate
DL-Aminoacid Oxidase	DL-Aminoacid

[0026] In an illustrative reaction, glucose oxidase catalyzes the interaction of Beta-D-glucose, water and oxygen during oral application of the adhesive to produce hydrogen peroxide and gluconic acid.

[0027] Glucose oxidase is characterized in the literature as a glycoprotein containing two molecules of flavine-adenine dinucleotide which has a molecular weight of approximately 150,000, an isoelectric point at pH 4.2 and an optimum pH at 5.5 with a broad pH range from 4 through 7.

[0028] The oxidizable substrate is generally present in the adhesive composition in an amount from about 0.015 to about 0.6 millimole per gram of adhesive composition and, preferably, in an amount from about 0.025 to about 0.1 millimole per gram of adhesive composition while the oxidoreductase enzyme specific to the substrate is generally present in the composition in an amount from about 0.5 to about 500 International Units (herein sometimes abbreviated IU) per gram of composition, and, preferably, in an amount from about 10 to about 40 IU per gram of composition. The term millimole identifies that quantity in grams corresponding to the molecular weight of the composition divided by one thousand. The term International Unit(s) identifies that amount of enzyme that will effect catalysis of 1.0 micromole of substrate per unit at pH 7.0 and 25 C. Oxidoreductase enzymes are supplied in dry or liquid form with the label specifying the concentration in International Units on a per gram or per milliliter, as appropriate.

[0029] In addition to the first enzyme system comprising oxidizable substrate and oxidoreductase enzyme specific to such substrate for producing hydrogen peroxide, the enzymatic adhesive composition of this invention is provided with a second enzyme system containing a peroxidatic peroxidase and an alkali metal salt of an oxygen accepting anion for interacting with hydrogen peroxide to produce an oxidized anionic bacterial inhibitor.

[0030] Peroxidases which can be used in the practice of this invention include lactoperoxidase, horseradish peroxidase, iodine peroxidase, and myeloperoxidase. Oxidizable salts which can be used in the practice of this invention include, for example, the thiocyanate, chloride or iodide salt of sodium, potassium, ammonium, calcium or magnesium or mixtures of such salts. In the presence of hydrogen peroxide, the oxygen accepting anion of the aforesaid salts, namely, thiocyanate, chloride or iodide, are oxidized to hypochlorite, hypochlorite and hypiodite, respectively.

[0031] Lactoperoxidase is a glycoprotein which, in one commercial embodiment, is a lyophilized powder derived from milk. This commercial peroxidase has an activity of 80 IU/mg and a projected molecular weight of 93,000 for L-Tyrosine iodination. The physical-chemical properties reported for lactoperoxidase include: molecular weight 93,000; partial specific volume 0.74; and heme/mole 1.0.

[0032] The peroxidase is generally present in the adhesive composition in an amount from about 0.05 to about 20 International Units per gram of composition and, preferably, in an amount from about 0.1 to about 1.0 International Units per gram of composition while the oxidizable salt is generally present in the composition in an amount from about

0.0001 to about 0.01 millimole per gram of composition and, preferably, in an amount from about 0.001 to about 0.006 millimole per gram of composition.

[0033] The operable integrity of the enzymatic system can be affected by catalase which is present in commercial glucose oxidase as well as mucous membrane tissue. Catalase, which is extraneous to the enzymatic system of this invention, competes with peroxidatic peroxidase for hydrogen peroxide. In order to reduce loss of hydrogen peroxide through the presence of catalase, an effective amount of enzymatic inhibitor specific to catalase can be advantageously incorporated into the enzymatic adhesive. An ascorbic salt such as sodium ascorbate, potassium ascorbate, ascorbyl palmitate, or mixtures thereof can be used as an enzymatic inhibitor which is specific to catalase. An effective amount of ascorbate salt for catalase inhibition is from about 0.000001 to about 0.0001 millimole per gram of adhesive composition. Iron salts such as ferrous sulfate can be incorporated into the enzymatic composition as a potentiator for ascorbate salt in its role as catalase inhibitor.

[0034] The enzymatic adhesive compositions of this invention may advantageously be formulated with an amino-hexose as, for example, an aminoglucose such as glucosamine, N-actyl glucosamine or mixtures thereof in order to increase the yield or accumulation of oxidized anionic bacterial inhibitor. The aminoglucose is generally present in the enzymatic composition in an amount from about 0.0001 to about 0.002 millimole per gram of adhesive and, preferably, in amount from about 0.003 to about 0.001 millimole per gram of adhesive.

[0035] As a result of the high viscosity of the enzymatic adhesives provided by the thickeners, the adhesives can be formulated with water in excess of 10 wt. % without initiating an enzymatic reaction prior to oral application of the adhesive. Water is generally present in the enzymatic adhesive in an amount from about 10 wt. % to about 60 wt. %, with an intermediate amount being from about 10 wt. % to about 50 wt. % and a preferred amount being from about 15 wt. % to about 35 wt. %.

[0036] In addition to the thickeners, enzyme system and water, the adhesive compositions of this invention may contain typical formulating ingredients such as humectants, buffering agents, fluorides, flavors, colors and sweeteners as well as a variety of auxiliary adhesive components as described in the above identified patents, the disclosures of which are incorporated by reference, together with the limitations as specified therein.

[0037] The enzymatic adhesives, in the form of a paste or gel, can be prepared in any suitable manner as, for example, by blending the dry ingredients into the liquid ingredients, with agitation, until a smooth mixture is obtained, with the proviso that shear sensitive ingredients, which include the enzymes, are added last to minimize shear impact on such ingredients.

[0038] In accordance with this invention, it has now been found that oxidoreductase enzyme stability can be maintained in an aqueous denture adhesive that contains in excess of 10 wt. % water, as shown by the examples hereinafter set forth, when a thickener is used in the aqueous adhesive so as to provide a viscosity of at least about 300,000 centipoises.

EXAMPLE 1

[0039] This example illustrates an aqueous, enzymatic denture adhesive containing 10 wt. % water together with an enzyme system containing Beta-D-glucose, glucose oxidase, lactoperoxidase and potassium thiocyanate.

Composition	Weight, grams
Glycerine	77.0000
D.I. Water	10.0000
Xanthan gum	4.0000
Carboxymethylcellulose	8.0000
Lactoperoxidase (100 IU/mg)	0.0005 (50 IU)
Beta-D-glucose	1.0000
Glucose oxidase (100 IU)	0.0010 (100 IU)
Potassium thiocyanate	0.1500
	100.1515

[0040] The viscosity of this enzymatic adhesive is 300,000 centipoises and the adhesive has an enzymatic shelf life in excess of 2 years.

EXAMPLE 2

[0041] This example illustrates an aqueous, enzymatic denture adhesive containing 15 wt. % water together with an

EP 1 334 710 A1

enzyme system containing Beta-D-glucose, glucose oxidase, lactoperoxidase and potassium thiocyanate wherein the thickener is a combination of polyacrylic acid (Carbopol 980) and hydroxymethyl cellulose.

Composition	Weight, grams
Glycerine	42.0000
Sorbitol (70 % solids, 30 % water)	50.0000
Carbopol 980	3.0000
Hydroxymethylcellulose	3.0000
Beta-D-glucose	1.0000
Lactoperoxidase (100 IU/mg)	0.0005 (50 IU)
Glucose oxidase (100 IU)	0.0010 (100 IU)
Potassium thiocyanate	0.1500
Sodium hydroxide	1.0000
	100.1515

[0042] The viscosity of this enzymatic adhesive is 400,000 centipoises and the adhesive has an enzymatic shelf life in excess of 3 years.

EXAMPLE 3

[0043] This example illustrates an aqueous, enzymatic denture adhesive containing 10 wt. % water together with an enzyme system containing hexose, hexose oxidase, myeloperoxidase and potassium thiocyanate wherein the thickener is a combination of polyacrylic acid (Carbopol 980) and hydrogenated starch.

Composition	Weight, grams
Glycerine	10.0000
D.I. Water	10.0000
Hydrogenated starch	67.0000
Carbopol 980	4.0000
Hexose (100 IU/mg)	7.0000
Hexose oxidase (100 IU/mg)	0.0001 (10 IU)
Myeloperoxidase (100 IU/mg)	0.0002 (100 IU)
Potassium thiocyanate	0.1500
Sodium hydroxide	2.0000
	100.1503

[0044] The viscosity of this enzymatic adhesive is 600,000 centipoises and the adhesive has an enzymatic shelf life in excess of 2 years.

EXAMPLE 4

[0045] This example illustrates an aqueous, enzymatic denture adhesive containing 57 wt. % water together with an enzyme system containing Beta-D-glucose, glucose oxidase, myeloperoxidase and potassium thiocyanate wherein the thickener is a combination of polyacrylic acid (Carbopol 980) and hydrogenated starch.

Composition	Weight, grams
D.I. Water	57.000
Hydrogenated starch	27.000
Carbopol 980	2.000
Polyvinylpyrrolidone	8.000
Beta-D-glucose	5.000
Glucose oxidase (100 IU/mg)	0.005 (500 IU)
Myeloperoxidase (100	0.001 (100 IU)

(continued)

Composition	Weight, grams
Potassium thiocyanate	0.150
Sodium hydroxide	1.000
	100.150

[0046] The viscosity of this enzymatic adhesive is 900,000 centipoises and the adhesive has an enzymatic shelf life in excess of 2 years.

EXAMPLE 5

[0047] This example illustrates an aqueous, enzymatic denture adhesive containing 14 wt. % water together with an enzyme system containing Beta-D-glucose, glucose oxidase, lactoperoxidase and potassium iodide wherein the thickener is a combination of hydrogenated starch, polyacrylic acid (Carbopol 980), and polyvinylpyrrolidone.

Composition	Weight, grams
D.I. Water	14.000
Glycerine	14.000
Hydrogenated starch	62.500
Carbopol 980	1.000
Polyvinylpyrrolidone	8.000
Sodium hydroxide	0.050
Beta-D-glucose	0.050
Glucose oxidase (100 IU/mg)	0.008
Lactoperoxidase (100 IU/gm)	0.010
Potassium iodide	0.004
	99.6184

[0048] The viscosity of this enzymatic adhesive is 1,900,000 centipoises and the adhesive has an enzymatic shelf life in excess of 3 years.

[0049] Adjunct antibacterial agents such as the enzyme lysozyme and the protein lactoferrin can also be added to the enzymatic formulations of this invention.

[0050] In view of the foregoing description and examples, it will become apparent to those of ordinary skill in the art that equivalent modifications thereof may be made without departing from the spirit and scope of this invention.

Claims

1. An aqueous, enzymatic denture adhesive composition having a water content of at least about 10 wt. % and containing, per gram of adhesive, from about 0.015 to about 0.6 millimole of oxidizable substrate and from about 0.5 to about 5,000 International Units of oxidoreductase enzyme specific to such substrate for producing hydrogen peroxide upon oral application of the adhesive; and
further containing non-toxic, ambient, water soluble thickener in an amount to provide the adhesive with a viscosity from about 300,000 to about 1,900,000 centipoises to thereby stabilize the adhesive against the production of hydrogen peroxide prior to oral application of the adhesive.
2. The denture adhesive of claim 1 wherein the amount of water soluble thickener is so selected as to provide the adhesive with a viscosity from about 400,000 to about 1,750,000 centipoises.
3. The denture adhesive of claim 1 wherein the amount of water soluble thickener is so selected as to provide the adhesive with a viscosity from about 600,000 to about 1,800,000 centipoises.
4. The denture adhesive of claim 1 wherein the upper limit of the water content is about 60 wt. %.

5. The denture adhesive of claim 1 wherein the water content is from about 10 wt. % to about 50 wt. %.
6. The denture adhesive of claim 1 wherein the water content is from about 15 wt. % to about 35 wt. %.
- 5 7. The denture adhesive of claim 1 wherein the water soluble thickener is selected from natural and synthetic hydrocolloids and mixtures thereof.
8. The denture adhesive of claim 1 wherein the water soluble thickener is a member selected from the group consisting of gum arabic, gum tragacanth, gum karaya, gum guar, xanthan gum, high viscosity starch, hydrogenated starch, carboxymethylcellulose, hydroxymethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, carboxyvinyl polymer, polyacrylic acid, polyacrylamide, ethylene oxide polymers and mixtures thereof.
- 10 9. The denture adhesive of claim 1 wherein the oxidizable substrate is Beta-D-glucose and the oxidoreductase enzyme is glucose oxidase.
- 15 10. The denture adhesive of claim 1 wherein the oxidizable substrate is hexose and the oxidoreductase enzyme is hexose oxidase.
11. The denture adhesive of claim 1 wherein the oxidizable substrate is present in an amount from about 0.025 to about 0.1 millimole per gram of adhesive and the oxidoreductase enzyme specific to the substrate is present in an amount from about 10 to about 1,000 International Units per gram of adhesive.
- 20 12. The denture adhesive of claim 1 which further contains an effective amount of an augmenting anti-bacterial agent selected from the group consisting of lysozyme, lactoferrin and mixtures thereof.
- 25 13. The denture adhesive of claim 1 which also contains, per gram of adhesive, from about 0.1 to about 10,000 International Units of peroxidatic peroxidase selected from the group consisting of lactoperoxidase, horse radish peroxidase, iodide peroxidase, chloride peroxidase, myeloperoxidase and mixtures thereof, and from about 0.0001 to about 0.01 millimole of an alkali metal salt of an oxygen accepting anion selected from the group consisting of thiocyanate, chloride, and iodide and mixtures of such salts for interacting with hydrogen peroxide to produce oxidized anionic bacterial inhibitor.
- 30 14. The denture adhesive of claim 13 wherein the peroxidase is present in an amount from about 10 to about 1,500 International Units per gram of adhesive and the oxidizable salt is present in an amount from about 0.001 to about 0.006 millimole per gram of adhesive.
- 35 15. The denture adhesive of claim 13 wherein the peroxidase is lactoperoxidase and the alkali metal salt is alkali metal thiocyanate.
- 40 16. The denture adhesive of claim 13 wherein the oxidizable substrate is Beta-D-glucose, the oxidoreductase enzyme is glucose oxidase, the peroxide is lactoperoxidase, the oxidizable salt is potassium thiocyanate, and the thickener is a combination of polyvinylpyrrolidone and polyacrylic acid.



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EUROPEAN SEARCH REPORT

Application Number
EP 02 25 5880

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	US 5 989 526 A (AASLYNG DORRIT ET AL) 23 November 1999 (1999-11-23) * column 3, line 35 - line 58; claims 1,14,15 * * column 6, line 52 - line 60 * * column 8, line 40 - line 44 * * column 9, line 31 - line 40 * ---	1-16	A61K6/00
D,A	US 4 564 519 A (MONTGOMERY ROBERT E ET AL) 14 January 1986 (1986-01-14) * column 6, line 47 - line 59; claim 1; examples * ---	1-16	
D,A	US 5 176 899 A (MONTGOMERY ROBERT E) 5 January 1993 (1993-01-05) * claims 1,4-10,16,17,20 * ---	1-16	
D,A	US 5 453 284 A (PELLICO MICHAEL A) 26 September 1995 (1995-09-26) * claims 1,8-11,13; examples * -----	1-16	
			TECHNICAL FIELDS SEARCHED (Int.Cl.7)
			A61K
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 16 April 2003	Examiner Pregetter, M
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	

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**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 02 25 5880

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

16-04-2003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5989526 A	23-11-1999	AU 724729 B2	28-09-2000
		AU 6732696 A	12-03-1997
		CA 2229715 A1	27-02-1997
		CN 1196674 A	21-10-1998
		WO 9706775 A1	27-02-1997
		EP 0844864 A1	03-06-1998
		JP 2000506490 T	30-05-2000
		US 6379653 B1	30-04-2002
US 4564519 A	14-01-1986	US 4537764 A	27-08-1985
		DE 3480691 D1	18-01-1990
		EP 0133736 A2	06-03-1985
		KR 9102667 B1	03-05-1991
		JP 1740554 C	15-03-1993
		JP 4025924 B	06-05-1992
		JP 59231011 A	25-12-1984
US 5176899 A	05-01-1993	AU 679169 B2	26-06-1997
		AU 3147193 A	28-06-1993
		CA 2124336 A1	10-06-1993
		EP 0614352 A1	14-09-1994
		JP 7563707 T	20-04-1995
		WO 9310752 A1	10-06-1993
		US 5270033 A	14-12-1993
		US 5262151 A	16-11-1993
US 5453284 A	26-09-1995	US 5336494 A	09-08-1994

EPD COMPT 10/98

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82